REMARKS

The specification is amended, hereby, to recite the §371 priority.

Claims 16-24, presented hereby in place of claims 12-15, are pending. Claims 9-11 stand withdrawn pursuant to restriction.

Present generic claim 16 corresponds to claim 14, and claims 18 and 19 correspond to claims 15 and 13, respectively, made dependent on claim 16, revised as explained below. Support for other presented claims can be found in the specification as follows:

- claim 17: page 2, line 38 - page 3, line 11;
- claims 20, 21: page 5, lines 24-27 and line 33 - page 6, line 7;
- claim 23: page 8, lines 14-17; and
- claim 24: page 8, lines 33-36.

The invention relates to a method for the chemotherapeutic treatment of a tumor in a patient with at least one cytotoxic agent, which method comprises the administration, during the treatment with the cytotoxic agent, of a therapeutically effective quantity of an isoflavonoid or of an analogue of the chromone type.

The invention thus takes advantage of the fact that the isoflavonoids or analogues of the chromone type unexpectedly increase the cytotoxic activity of conventional cytotoxic drugs, when combined therewith.

Reconsideration is requested with respect to the rejection under 35 USC 112, first paragraph for alleged lack of enablement.

Claims 12 and 13 are rejected because the term "an isoflavonoid or an analogue of the chromone type" are allegedly too broad in view of the instant specification.

To forward prosecution, claims 16-24 are limited to isoflavonoids of formula I, i.e., as in claim 14.

According to the statement of rejection, the specification would support for "vincristine" but not the broader term "cytotoxic agent." On the contrary, Applicants submit that claiming the use of "cytotoxic agent" is justified, since the requirements of §112, paragraph 1, are satisfied in the present case.

Lack of enablement under §112 of the statue is not established by mere allegations that terminology is overly broad. *Horton v. Stevens*, 7 USPQ2d 1245 (BPA&I 1988). Satisfaction of the enablement requirement does not require the specification to contain a single working example. *In re Strahilevitz*, 212 USPQ 1 (CCPA 1982). "Mention of representative compounds encompassed by generic claim language clearly is not required by §112 or any other provision of the statute." *In re Robins*, 166 USPQ 552, 555 (CCPA 1970)."[I]t is not necessary to . . . describe in the specification all possible forms in which the claimed principle may be reduced to practice." *Smith v. Snow*, 294 U.S. 1, 11 (1935). Under §112, first paragraph, the concern of the USPTO is support or non-support for a generic term, not its breadth. *In re Marcozzi*, 169 USPQ 367, 369 (CCPA 1971).

Lack of enablement is not demonstrated merely because the claim scope might, theoretically, cover embodiments that do not work; the function of the claims is not to specifically exclude

possibly inoperative embodiments. *Atlas Powder v. E.I. du Pont de Nemours Co.*, 224 USPQ 409 (Fed. Cir. 1984). Section 112 enablement is satisfied when generic claims cover thousands of end products, some of which may not be operative (i.e., may not work for the stated purpose of the claimed invention). Id. The Federal Circuit and its predecessor courts have repeatedly held that the mere presence of some non-working embodiments within a generic claim does not justify a rejection for lack of enablement under §112, first paragraph.

> As we have said before, it is almost always possible to so constr. a claim as to have it read on non-working embodiments, In re Cook, 58 CCPA 1049, 1054, 439 F.2d 730, 734, 169 USPQ 298, 301 (1971), but the alternative of requiring an applicant to be so specific in his claims "as to exclude materials known to be inoperative and [which] even those *not* skilled in the art would not try would result in claims which would fail to comply with 35 U.S.C 112, second paragraph, because they would be so detailed as to obscure, rather than to particularly point out and distinctly claim, the invention. In re Meyers, 56 CCPA 1129, 410 F.2d 420, 161 USPQ 668 (1969), quoted with approval in In re Anderson, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973).

In re Smythe, 178 USPQ 279, 286 (CCPA 1973)(*emphasis in original*).

Moreover, while working examples drawn to specific embodiments may be desirable, they are not *required* in order to satisfy enablement under §112. *In re Strahilevitz*, 212 USPQ 561 (CCPA 1982). It is well established that working examples are not necessary when one possessed of knowledge of ordinary skill in the art could practice the invention without the exercise of undue experimentation. *Ex parte Nardi*, 229 USPQ 79 (BPA & I 1986). "In satisfying the enablement requirement, an application need not teach, and preferably omits, that which is well known in the art." *Staehelin v. Secher*, 24 USPQ2d 1513, 1516 (BPA & I 1992).

One skilled in the art generally defines classes of cytotoxic agents according to the mechanism of action responsible for the anti-tumoral activity of these agents. As explained in the present specification (page 6, line 35 to page 8, line 13), cytotoxic drug classes include for instance intercalating agents, alkylating agents, anti-metabolic agents, topoisomerase inhibitors, etc.

Attention is directed to the examples of the present application, in which the biological effects of the combined administration of a cytotoxic agent and an isoflavonoid presently claimed are assessed. Three combinations of an isoflavonoid with a cytotoxic agents were assayed *in vivo* in murine tumor xenograft models of carcinoma (MXT-HS) or lymphoma (P388 sc). Each of the cytotoxic agent assayed pertains to a different class of cytotoxic agents, as defined according to the mechanism responsible for their biological activity.

In these experiments, a significant increase in survival time and/or in tumor size reduction is observed with the cytotoxic agent/isoflavonoid combination compared with the cytotoxic agent or the isoflavonoid used alone (Tables III and IV in the present application, pages 20-21).

Therefore, the instant application provides sufficient evidence that use of the isoflavonoid as presently claimed potentiates the cytotoxic activity of cytotoxic agents, in general, whatever the mechanism of action. The *in vivo* experiments described provide more than adequate support that the presently claimed invention is enabled for a "cytotoxic agent," generically. Withdrawal of the rejection under 35 USC 112, paragraph 1, is in order.

Reconsideration is requested with respect to the rejection under 35 USC 112, paragraph 2, based on the claims not reciting the amount of "cytotoxic agent." Applicants submit there is no need to specify the amount of cytotoxic agents used to meet §112, second paragraph, requirements.

According to the statement of rejection, the term "at least one cytotoxic agent" in claims 12-15, is indefinite. This term has been changed to "a cytotoxic agent" in present claims 16-24. This change does not change the scope fo the claim. The indefinite article "a" appearing in a claim means *one or more than one*, unless qualified. *KJC Corp. v. Kinetic Concepts Inc.* * USPQ2d * , * (Fed. Cir. 2000). While claims are to be given their broadest reasonable interpretation during prosecution, the definition of a claim limitation given by the Examiner cannot be different than would be given by one of ordinary skill in the art. *In re Cortright*, 49 USPQ2d 1464 (Fed. Cir. 1999).

As such, the change to "a" does not limit the claims to the embodiment wherein one cytotoxic agent only is administered together with an isoflavonoid.

Actually, combinations of cytotoxic agents are often used in chemotherapy of cancer (see for instance navelbine + cisplatine or cyclophosphamide + doxorubicin + vincristine (page 23), cisplatine + etoposide (page 24), etc...).

The statement of rejection is of the opinion that the claimed method should specify the amount of cytotoxic agent used. Applicant disagrees.

The statement of rejection confuses the function of the claims, on the one hand, with the function of the specification, on the other; the claims define the legal limits of the invention, the specification details *how* the invention is to be *practiced*. *In re Roberts*, 176 USPQ 313, 315 (CCPA

1973). *How* much of a particular ingredient is needed for the presently claimed invention to be *practiced* is a function of the instant specification; it need not be recited in the claims. It "is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter." *Bendix Corp. v. United States*, 204 USPQ 617, 621 (Ct. Cl. 1979). Reciting "an effective amount" in conjunction with a pharmaceutical composition is sufficient under §112, ¶2. *Ex parte Skuballa*, 12 USPQ2d 1570 (Bd. Pat. App. & Inter. 1989).

Actually, it would be apparent for the skilled person that the cytotoxic agent is administered to the patient in accordance with the chemotherapeutic protocols classically used in cancer therapy. This is consistent with the examples of treatment modality shown on page 23 and followings. For each modality, reference is made to a recommended protocol of administration of the cytotoxic agent(w) to which isoflavonoid administration is further combined (see for instance page 23, lines 11-5 and lines 20-23, page 24, lines 3-5, page 25, lines 5-7, etc). Thus, one skilled in the art would readily contemplate that, in the claimed method, the cytotoxic agent(s) is/are to be administered as usually practiced in chemotherapy of cancer.

As recognized in the statement of rejection, efficiency of the treatment combining genistein (20 mg/kg) with vincristine (0.63 mg/kg) is clearly demonstrated in the specification. One skilled in the art would readily know how to adapt this dose regimen according to the patient and the cytotoxic agent(s) to be used.

The term "chosen from" is not used in claims 16-24 and, instead, more accepted Markush language is employed.

Reconsideration is requested concerning the rejection of claims 12-15 as being allegedly unpatentable over the combined teachings of Weber et al., and WO 97/46531.

Actually, Weber et al., describes a process for manufacturing genistein. This compound is further described as reducing DMBA induced tumors by 50%. Therefore, this document basically teaches that genistein may have some antitumor activity.

As to WO 97/46531, it relates to a method of treatment of cancer using pyridine derivative, that show reduced side effects. WO 97/46531 contemplates the combined administration of said pyridine derivative with another chemotherapeutic agent (p. 11, l. 33-37), in particular vincristine (p. 12, l. 18 and claim 20). The reference, thus, teaches only that two chemotherapeutic agents may be combined.

The conclusion drawn by the statement of rejection in view of these documents is that one skilled artisan provided in the art would have been motivated to combine an isoflavonoid, genistein for instance, with an antitumor agent. The statement of rejection further alleges that the results of this combination show no more than additive effects, except for a dosage of 20 mg/kg genistein with 0.63 mg/kg vincristine.

First of all, as recognized in the statement of rejection, there is no explicit incentive for the skilled in the cited prior art documents to specifically combine an isoflavonoid compound with cytotoxic agents. Thus, the is no obviousness under §103(a). When the claimed invention requires modification of the prior art, there is no obviousness under §103 when "[t]he prior art does not

suggest . . . modification of the . . . [prior art], or provide any reason or motivation to make the modification." *In re Laskowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989).

Furthermore, one skilled in the art could not have expected that isoflavonoids would potentiate cytotoxicity of the conventional cytotoxic agents.

Actually, contrary to the statement of rejection's assertion, the teachings of the present application clearly demonstrate that the cytotoxic agents do exhibit increased cytotoxicity when combined with an isoflavonoid, as explained above. The effects of combined treatments were evidenced *in vivo* on the mean survival time and/or the tumor volume parameters as compared to the cytotoxic agent or the isoflavonoid compound give alone.

Attention is directed to Example 4 of the specification. More particularly, the results shown in Table III (page 20) show that the isoflavonoid "genistein", when associated with a cytotoxic agent chosen from cyclophosphamide, vincristine or etotoposide, significantly increases the mean survival time of model animals, as compared to genistein alone or to the cytotoxic agent alone.

Similarly, Table IV (page 21) illustrates that genistein has synergistic effects with etoposide as regard to the reduction of tumor volume. As observed, genistein alone has no effect on tumor growth. However, the combined administration of genistein (G) plus vincristine (VCR) or genistein (G) plus etoposide (ETO), decreases the tumor volume by about 1.4 fold (G + VCR) and 2 fold (G + ETO), respectively, when compared to the cytotoxic agent given alone.

Altogether, the experimental data provided in the present application clearly demonstrate that the observed cytotoxic activity is not a mere addition of the respective cytotoxic effects of the

isoflavonoid and the cytotoxic agent, but rather that isoflavonoids potentiate the activity of the cytotoxic agent in a synergistic manner. Where the invention combines elements not combined in the prior art and results in a synergistic effect, i.e., a greater than additive result, this provides a sufficient showing of nonobviousness under §103. *In re Corkill*, 226 USPQ 1005 (Fed. Cir. 1985).

In no way would, or could, the skilled artisan expect such a result. Accordingly, the analysis in the statement of rejection is not supported by the facts of record and the invention of claim 14, and the present claims is not obvious over the combination of Weber et al., and WO 97/46531.

Request for Acknowledgment of Foreign Priority Under 35 USC 119

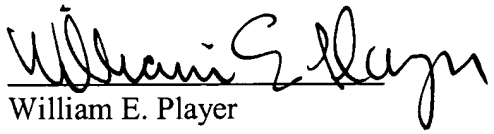
A claim to foreign priority under 35 USC 119 has been made (inventorship declaration, filed July 15, 1998) and the certified copy of the priority document received by the PTO (Notification of Acceptance, mailed July 13, 1999 by the PTO, and Form PCT/IB304, mailed 12 August 1999 by the International Bureau).

Accordingly, request is made that the Examiner mark the next Office Action to acknowledge, both, the claim to §119 priority and receipt of the certified copy.

Favorable action is requested.

Respectfully submitted,

JACOBSON·HOLMAN PLLC

By: 
William E. Player
Reg. No. 31,409

400 Seventh Street, N.W.
The Jenifer Building
Washington, D.C. 20004
Tel.: (202) 638-6666
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WEP/rdt
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